Synthesis of Esters of Lipophilic Proline Analogs by Reduction of Ethyl 5,6-Dihydro-4*H*-1,2-oxazine-3-carboxylates

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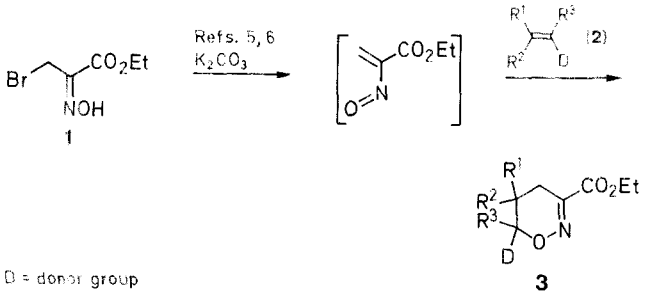
Dedicated to Prof. W. Bartmann on the occasion of his 60th birthday.

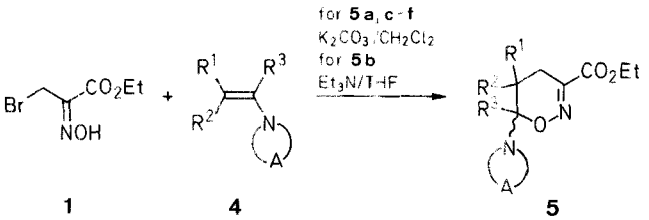
Ethyl esters of proline substituted with lipophilic residues in 4- and/or 5-position are obtained via catalytic hydrogenation of the corresponding ethyl 5,6-dihydro-4*H*-1,2-oxazine-3-carboxylates.

For a number of years, we have been engaged in the synthesis of lipophilic analogs of proline in connection with our work on inhibitors of angiotensin converting enzyme (ACE).[1-4] A recent communication by Gilchrist et al.[5] prompts us to describe our own work on the reduction of 5,6-dihydro-4*H*-1,2-oxazine-3-carboxylates **3**, which leads to compounds of this type. The cycloaddition of ethyl 2-nitrosopropenoate, generated *in situ* from ethyl 3-bromo-2-hydroxyiminopropanoate (**1**) and base, with electron-rich alkenes **2** provides an elegant access to these compounds[6-8] (Scheme **A**).



Scheme **A**

Using enamines **4**, ethyl 6-amino-5,6-dihydro-4*H*-1,2-oxazine-3-carboxylates **5a, c–f** were prepared (Scheme **B**, Table 1). A disadvantage of the described methodology is the use of a 3 to 10-fold excess of alkene **2** or enamine **4**, which is not feasible for more valuable compounds in the course of an extended synthetic route. We have modified the reaction conditions by the addition of triethylamine to equimolar amounts of **1** and enamines **4** on large scale in anhydrous tetrahydrofuran as exemplified for **5b** (Scheme **B**, Table 1). Best results were obtained with pyrrolidine or morpholine enamines.

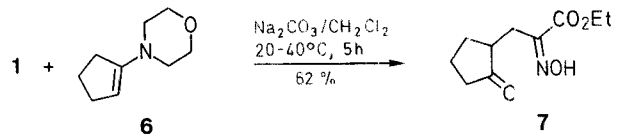


4, 5	R^1	R^2	R^3	N–A
a	*n*-C_5H_{11}	*n*-C_5H_{11}	H	N
b			H	N
c			H	N
d			H	N
e	H	$(CH_2)_{10}$		N O
f	H	Ph	Ph	N O

Scheme **B**

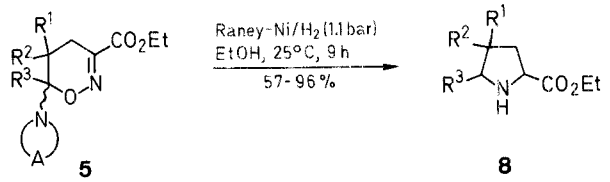
In Table 1 it can be seen that enamines of aldehydes (entries **5a–d**) and ketones (entries **5e, f**) can be used with equal success. Compounds **5b** and **5e, f** are obtained as mixtures of diastereoisomers. For **5b**, a ratio of 10:1 can be deduced from the signals of the proton on C-6 in the ^{1}H-NMR spectrum. For compounds **5e, f**, derived from ketones, determination of the ratios was not possible either from ^{1}H-NMR or TLC. Isomers were not separated.

With 1-morpholinocyclopentene (**6**), the reaction takes a similar course as in the case of **1** with electron-rich heterocycles;[6] alkylated cyclopentanone **7** is obtained in 62% yield (Scheme **C**).



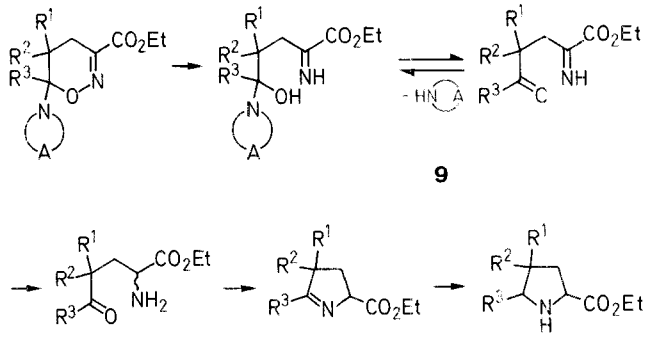
Scheme C

Hydrogenation of compounds **5** with Raney-nickel under neutral conditions[9] led to the desired amino acid esters **8** (Scheme **D**) in good yield (Table 2).[10]



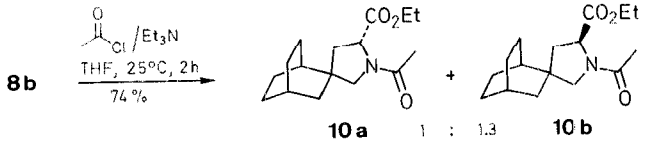
Scheme D

This transformation requires three consecutive reduction steps and one cyclization in between. In accord with Gilchrist's proposal,[5] we assume that N–O cleavage is the first step of the sequence followed by reduction of the imine **9** and cyclization to the Δ^1-pyrroline, which is again reduced (Scheme **E**).



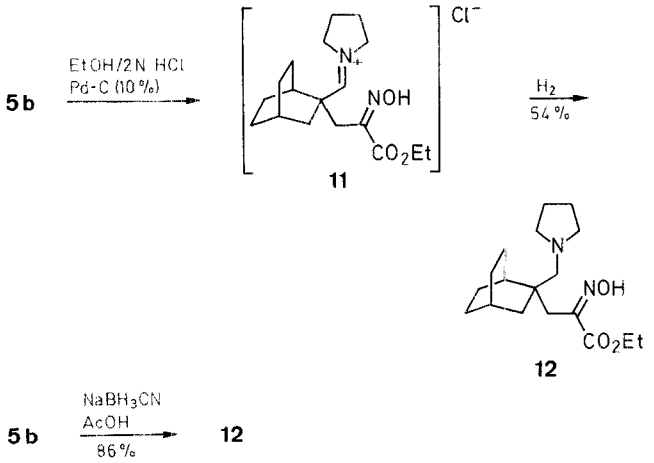
Scheme E

Since addition of hydrogen to imine **9** can occur from either side, formation of a mixture of diastereoisomers for esters **8** can be expected, wherever possible. Indeed, in the case of **8b** two isomers are formed in a ratio of 1:1.3, as determined by separation of their respective *N*-acetyl derivatives **10a** and **10b** (Scheme **F**).



Scheme F

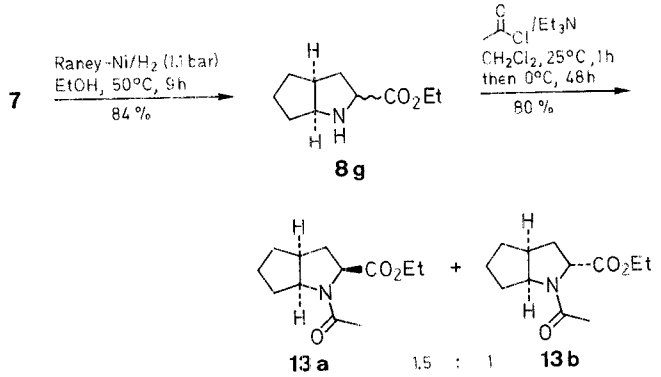
However, in the case of **8f** only the respective *cis-endo*-isomers are formed, probably due to large steric interference of the two phenyl rings upon interaction with the catalyst surface. Using **5b** the reduction conditions were extensively varied to obtain optimum yield and stereoselectivity. With palladium on charcoal, only very slow reduction occured under neutral or acidic conditions. In acetic acid/2 N hydrochloric acid, **8b** was obtained in 80% yield. In hydrogen chloride/ethanol as solvent, **8b** was only a minor by-product, while the main reaction took a different course giving rise to compound **12** in 54% yield (Scheme **G**).



Scheme G

In accord with the behavior of similar compounds,[11] we suggest that oxygen protonation is followed by C–O bond cleavage and subsequent hydrogenation of iminium salt **11**. The same product is obtained in 86% yield with sodium cyanoborohydride in acetic acid.

Ketooxime **7** can also be converted to the respective proline analog **8g** by catalytic hydrogenation. With Raney-nickel in ethanol at 50 °C, **8g** is obtained in 84% yield. The *endo/exo* ratio was determined by conversion to the acetamides **13a** and **13b**, which are easily separated by chromatography (Scheme **H**). The configuration was determined by comparison with authentic samples prepared by independent routes.[10]



Scheme H

Compounds **5** are converted in few steps to highly potent inhibitors of angiotensin converting enzyme.

Ethyl 5,6-Dihydro-4*H*-oxazine-3-carboxylates 5; General Procedure Using Excess of Olefin Component:[5,6]

Ethyl 3-bromo-2-hydroxyiminopropanoate (10.5 g, 50 mmol) is dissolved in CH_2Cl_2 (200 mL). The required enamine (0.1 mol) is added at room temperature followed by K_2CO_3 (23.5 g, 0.17 mol). A slight warming to 35–40 °C is observed. After stirring at room temperature

for 3–5 h, the solids are removed by filtration, and the filtrate is concentrated. Chromatography on silica gel with the appropriate solvent (usually mixtures of EtOAc and cyclohexane (ratios of 1:1 to 1:4) gives pure products (Table 1).

Ethyl 2-Oximino-3-(2-oxo-cyclopentyl)propanoate (7):
Morpholinocyclopentene (**6**; 5 g, 32.7 mol) is reacted with ethyl 3-bromo-2-hydroxyiminopropanoate (2.3 g, 10.9 mmol) according to the general procedure described above. Compound **7** is obtained after chromatographic purification on silica gel; yield: 1.5 g (62%); mp 94–96°C [diisopropyl ether/petroleum ether (bp 40–60°C), 1:2].

$C_{10}H_{15}NO_4$ (213.2) calc. C 56.33 H 7.11 N 6.57; found 56.61 7.01 6.44

IR (KBr): ν = 3240 (=NOH); 1760, 1740 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$): δ = 1.38 (t, 3H, J = 7 Hz); 1.60–1.90 (m, 2H); 2.0–2.4 (m, 4H); 2.5–2.75 (m, 2H); 2.97 (dd, 1H, J = 6, 12 Hz); 4.32 (q, 2H, J = 7 Hz).

MS (EI): m/z = 213 (M^+, 5); 196 ($M^+ - OH$, 62); 168 (21); 167 ($M^+ - EtOH$, 29); 150 (23); 122 (100).

Ethyl 6′-(1-Pyrrolidinyl)spiro[bicyclo[2.2.2]octane-2,5′(6′*H*)-[4*H*-1,2]-oxazine]-3′-carboxylate (5b); Typical Procedure Using Equimolar Amounts of Reactants:
2-[2-(1-Pyrrolidinyl)-ethenyl]bicyclo[2.2.2]octane[13] (**4b**; 6.92 kg, 36.2 mol) is dissolved in THF (55 L), ethyl 3-bromo-2-hydroxyiminopropanoate (8.12 kg, 38.6 mol) is added in portions during 30 min, which causes the temperature to rise to 35–40°C. After stirring for 30 min, Et_3N (3.91 kg, 38.7 mol) is added during 45 min. Again a temperature rise to 40°C is observed. After stirring for 2 h, H_2O (15 L) is added with vigorous stirring. The organic layer is separated and dried (Na_2SO_4). After evaporation, toluene (5 L) is added, and the solution is evaporated to dryness. The crude product is purified by chromatography on silica gel (3 kg) with toluene as eluent; yield: 7.08 kg (61%); mp 113–115°C (Table 1).

Table 1. Compounds **5** Prepared

Compound	Yield (%)	Molecular Formula[a]	mp (°C)[b]	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, J(Hz)	MS (EI)[d] m/z (%)
5a	48[e]	$C_{21}H_{38}N_2O_3$ (366.6)	oil	0.9 (t, 6H, J = 6); 1.0–1.5 (m, 19H); 1.55–1.9 (m, 4H); 2.3 (s, 2H); 2.7–3.2 (m, 4H); 4.35 (q, 2H, J = 7); 4.7 (s, 1H)	366 (M^+, 7); 349 (75); 280 (32); 266 (24); 180 (100); 124 (20); 100 (81)
5b	61[f]	$C_{18}H_{28}N_2O_3$ (320.4)	113–115	1.1 (m, 1H); 1.4 (t, 3H, J = 7); 1.35–2.0 (m, 15H); 2.2 (d, 1H, J = 18); 2.6 (dd, 1H, J = 18, 2); 2.7 (m, 2H); 3.0 (m, 2H); 4.35 (m, 2H); 4.88, 4.95 (2d, 1H, J = 2)	320 (M^+, 5); 303 (30); 251 (30); 234 (25); 191 (100); 162 (33); 100 (45); 70 (35)
5c	65[e]	$C_{23}H_{24}N_2O_3$ (376.5)	58–60	1.4 (t, 3H, J = 7); 1.8–2.2 (m, 4H); 2.7 (br s, 1H); 3.2 (br s, 1H); 3.3–3.7 (m, 4H); 4.4 (q, 2H; J = 7); 5.2 (s, 1H); 7.2–7.7 (m, 8H)	–[g]
5d	59[e]	$C_{20}H_{28}N_2O_3$ (344.4)	oil	1.4 (t, 3H, J = 7); 1.5–2.2 (m, 24H); 2.8 (m, 2H); 3.05 (m, 2H); 3.22 (dd, 1H, J = 18, 2); 4.33 (m, 2H); 5.5 (d, 1H, J = 2)	344 (M^+, 5); 329 (35); 277 (55); 260 (30); 217 (60); 206 (20); 150 (100); 79 (65)
5e	89[e]	$C_{21}H_{35}N_2O_4$ (379.5)	158–159	1.0–1.5 (m, 23H); 2.4–2.8 (m, 5H); 3.0–3.2 (m, 1H); 3.45 (t, 4H, J = 4); 3.8–4.0 (m, 1H); 4.25 (q, 2H, J = 7)	–[g]
5f	62[e]	$C_{23}H_{26}N_2O_4$ (394.5)	165–167	1.40 (t, 3H, J = 7); 2.36 (dd, 1H, J = 18, 9); 2.62–2.72 (A part of AA′XX′ system, 2H); 2.88 (dd, 1H, J = 18, 6); 3.0–3.1 (A′ part of AA′XX′ system, 2H); 3.67 (XX′ part of AA′XX′ system, 4H); 3.85 (dd, 1H, J = 9, 6); 4.36 (q, 2H, J = 7); 6.88–7.0 (m, 4H); 7.13–7.23 (m, 6H)	394 (M^+, 100); 377 (20); 303 (40); 278 (70); 264 (70); 178 (30); 105 (92)

[a] Satisfactory microanalyses obtained: C ±0.36, H ±0.23, N ±0.32.
[b] Uncorrected, measured with a Büchi 510 apparatus.
[c] Recorded with either a Bruker WP-60 or a Bruker HX-270 spectrometer.
[d] Recorded on a AEI MS 30 spectrometer.
[e] Prepared using an excess of enamine component.
[f] Prepared using equimolar amounts of **1** and enamine.
[g] Not measured.

Table 2. Compounds **8** Prepared[a]

Compound	Isomer Ratio	Yield (%)	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
8a	–	96	$C_{17}H_{33}NO_2$ (283.5)	0.95 (t, 6H, J = 6); 1.1–1.8 (m, 19H); 1.8–2.2 (m, 2H); 2.8 (s, 2H); 3.9 (m, 1H); 4.3 (q, 2H, J = 7)
8b	57:43	85	$C_{14}H_{23}NO_2$ (237.4)	1.3 (2t, 3H, J = 7); 1.4–1.8 (m, 12H); 1.6–2.2 (m, 2H); 2.4 (br s, 1H); 2.7–3.0 (m, 2H); 3.7–4.0 (m, 1H); 4.2 (m, 2H)
8c	–	89	$C_{19}H_{19}NO_2$ (293.4)	1.35 (t, 3H, J = 7); 2.0 (m, 1H); 2.6 (m, 1H); 3.25, 3.55 (AB system, 2H, J = 11); 3.3–4.0 (m + br s, 2H); 4.3 (q, 2H, J = 7); 7.2–7.7 (m, 8H)
8d	–	95	$C_{16}H_{23}NO_2$ (261.4)	1.3 (t, 3H, J = 7); 1.4–2.0 (m, 14H); 2.0–2.5 (m, 2H); 3.3, 3.6 (AB system, 2H, J = 12); 4.3 (q, 2H, J = 7); 4.4 (m, 1H)
8e	–[c]	63	$C_{17}H_{31}NO_2$ (281.5)	1.0–1.5 (m, 23H); 1.7–2.1 (m, 2H); 2.2–2.6 (m, 2H); 2.8–3.05 (m, 1H); 3.6–3.9 (m, 2H); 4.2 (q, 2H, J = 7)
8f	95:5	57[d]	$C_{19}H_{21}NO_2$ (295.4)	1.37 (t, 3H, J = 7); 2.35 (dt, 1H, J = 13, 10); 2.52 (dt, 1H, J = 13, 8); 2.7–2.9 (br s, 1H); 3.74 (dt, 1H, J = 10, 8); 4.15 (dd, 1H, J = 10, 8); 4.35 (q, 2H, J = 7); 4.61 (d, 1H, J = 8); 6.8–6.9 (m, 2H); 6.95–7.1 (m, 8H)

[a] All compounds are oils, except **8f**, which has a mp of 66–68°C.
[b] Satisfactory microanalyses obtained: C ±0.32, H ±0.21, N ±0.34.
[c] Not determined.
[d] Hydrogenation at 70°C and 100 bar gives a 70% yield of **8f**.

Ethyl Prolinate Derivatives 8; General Procedure:
The appropriate ethyl 5,6-dihydro-4*H*-oxazine-3-carboxylate **5** (10 mmol) is added to a suspension of neutral Raney-nickel (~ 2 g) in EtOH (100 mL). The mixture is hydrogenated at 1.1 bar H_2 pressure and room temperature. After 9 h, ~ 600 mL (3 equiv) of H_2 are absorbed. After removal of the catalyst and evaporation, the product is purified by MPLC on silica gel with CH_2Cl_2/MeOH (9:1) as eluent. The product is obtained as a clear oil (R_f ~ 0.3), except for **6f**, which forms colorless crystals (Table 2).

Ethyl 1'-Acetylspiro[bicyclo[2.2.2]octane-2,3'-pyrrolidine]-5'-carboxylate (10a and 10b):
To a solution of **8b** (3.4 g, 14.2 mol) and Et_3N (2.9 g, 28.4 mmol) in absolute THF (150 mL) at 0°C is added acetyl chloride (1.3 g, 16.7 mmol) dropwise. After stirring for 2 h at room temperature, the precipitated salt is removed by filtration, and the filtrate is evaporated. The crude mixture of diastereoisomers is separated by flash chromatography on SiO_2 using EtOAc/cyclohexane (2:1) as eluent.

10a; yield: 1.27 g (32%); mp 122°C, R_f 0.4 (SiO_2; EtOAc/cyclohexane (4:1).

$C_{16}H_{25}NO_3$	calc.	C 68.78	H 9.02	N 5.01
(279.4)	found	69.10	8.84	5.20

^{1}H-NMR ($CDCl_3$) shows two amide bond rotamers (ratio 1:4).

Minor rotamer: δ = 1.30 (t, 3 H, J = 7 Hz); 1.3–1.8 (m, 12 H); 1.85 (dd, 1 H, J = 10, 12 Hz); 1.96 (s, 3 H); 2.31 (ddd, 1 H, J = 10, 12, 1.2 Hz); 3.14 (d, 1 H, J = 12 Hz); 3.88 (dd, 1 H, J = 12, 1.2 Hz); 4.2 (m, 2 H); 4.40 (dd, 1 H, J = 8, 10 Hz).

Major rotamer: δ = 1.28 (t, 3 H, J = 7 Hz); 1.3–1.8 (m, 13 H); 2.10 (s, 3 H); 2.20 (ddd, 1 H, J = 8, 12, 1 Hz); 2.37 (dd, 1 H, J = 12, 1 Hz); 3.92 (d, 1 H, J = 12 Hz); 4.2 (m, 2 H); 4.42 (dd, 1 H, J = 8, 12 Hz).

MS (EI): m/z = 279 (M^+, 6); 236 (2); 207 (10); 206 (70); 165 (14); 164 (100).

10b; yield: 1.66 g (42%); oil, R_f 0.32 (SiO_2; EtOAc/cyclohexane (4:1).

$C_{16}H_{25}NO_3$	calc.	C 68.78	H 9.02	N 5.01
(279.4)	found	68.58	8.78	5.32

^{1}H-NMR ($CDCl_3$) shows two amide bond rotamers (ratio 1:2).

Minor rotamer: δ = 1.33 (t, 3 H, J = 7 Hz); 1.4–1.8 (m, 12 H); 2.0 (s, 3 H); 2.15 (dd, 1 H, J = 12, 3.5 Hz); 2.25 (dd, 1 H, J = 10, 12 Hz); 3.5 (d, 1 H, J = 12 Hz); 3.57 (d, 1 H, J = 12 Hz); 4.25 (m, 2 H); 4.37 (dd, 1 H, J = 10, 3.5 Hz)

Major rotamer: δ = 1.29 (t, 3 H, J = 7 Hz); 1.4–1.8 (m, 12 H); 1.9 (dd, 1 H, J = 12, 6 Hz); 2.08 (s, 3 H); 2.25 (dd, 1 H, J = 10, 12 Hz); 3.4 (d, 1 H, J = 12 Hz); 3.55 (d, 1 H, J = 12 Hz); 4.2 (q, 2 H, J = 7 Hz); 4.45 (dd, 1 H, J = 10, 6 Hz).

MS (EI), m/z = 279 (M^+, 4); 236 (2); 207 (10); 206 (70); 165 (14); 164 (100).

2-(2-Ethoxycarbonyl-2-hydroxyimino)ethyl-2-(1-pyrrolidinyl)methylbicyclo[2.2.2]octane (12):

A. By Hydrogenation: To a solution of **5b** (1.5 g, 4.7 mmol) in EtOH (30 mL) and 2 N HCl (5 mL) is added Pd/C (10%, 300 mg), and the mixture is hydrogenated at room temperature and 1.1 bar pressure for 24 h. After removal of the catalyst and evaporation of EtOH, the solution is diluted with H_2O (50 mL), basified with 3% aq. $NaHCO_3$ (30 mL), extracted with CH_2Cl_2 (3 × 50 mL), and the extract is dried (Na_2SO_4). Evaporation gives a crude product showing two components on TLC (SiO_2, CH_2Cl_2/MeOH, 9:1; R_f = 0.3 corresponding to **8b**, and 0.2). Chromatographic separation (SiO_2, CH_2Cl_2/MeOH, 9:1) affords **8b**; yield: 90 mg (8%) and **12**; yield: 0.9 g (54%); mp 139–141°C (diisopropyl ether/*n*-hexane (1:2).

$C_{18}H_{30}N_2O_3$	calc.	C 67.55	H 9.38	N 8.69
(322.5)	found	67.22	9.51	8.51

^{1}H-NMR (270 MHz, $CDCl_3$/TMS): δ = 1.35 (t, 3 H, J = 7 Hz); 1.3–1.8 (m, 11 H); 1.9 (m, 4 H); 2.2 (m, 1 H); 2.39, 2.63 (AB System, 2 H, J = 12 Hz); 2.7 (m, 4 H); 2.78, 2.85 (AB System, 2 H, J = 12 Hz); 4.3 (m, 2 H); 14.8 (br s, 1 H).

MS (EI): m/z = 322 (M^+, 20); 305 (29); 277 (27); 249 ($M^+ - CO_2Et$, 100); 231 (56); 192 (100).

B. By Reduction with $NaBH_3CN$: To a solution of **5b** (0.64 g, 2 mmol) in AcOH (10 mL), $NaBH_3CN$ (0.4 g) is added in small portions. After stirring for 30 min, the mixture is poured into 10% aq. Na_2CO_3 (50 mL). The mixture is extracted with EtOAc (2 × 30 mL), the organic layer is dried (Na_2SO_4) and evaporated to give crystalline **12**; yield: 0.61 g (86%), identical with the material obtained above.

1-Acetyl-2-ethoxycarbonyloctahydrocyclopenta[*b*]pyrrole, *cis-endo*-(13a) and *cis-exo*-Isomers (13b):
Compound **7** (0.9 g, 4.2 mmol) is hydrogenated according to the general procedure of hydrogenation (see above) at 50°C. After removal of the catalyst by filtration, the crude oil (0.65 g, 3.5 mmol) is dissolved in a mixture of CH_2Cl_2 (5 mL) and Et_3N (0.49 mL, 3.5 mmol). To this mixture is added dropwise a solution of acetyl chloride (0.26 mL, 3.5 mmol) in CH_2Cl_2 (5 mL). After 1 h at room temperature and 48 h at 0°C, the solvent is removed, and the residue is triturated with EtOAc (30 mL) to remove $Et_3N \cdot HCl$. The filtrate is concentrated, and the isomers are separated by chromatography on silica gel with EtOAc as eluent to give **13a** (more polar) and **13b** (less polar) as colorless oils.

13a; yield: 290 mg (31%).

$C_{12}H_{19}NO_3$	calc.	C 63.97	H 8.52	N 6.22
(225.3)	found	64.23	8.40	5.95

^{1}H-NMR ($CDCl_3$): δ = 1.26 (t, 3 H, J = 7 Hz); 1.38–2.16 (m, 7 H); 1.9, 2.11 (2 s, ratio 1:5, 3 H); 2.31–2.56 (m, 1 H); 2.57–2.87 (m, 1 H); 4.1–4.28 (m, ~ 2.7 H); 4.37–4.52 (m, ~ 0.5 H); 4.57 (dd, 0.8 H, J = 10, 6 Hz), (mixture of rotamers, ratio 5:1).

MS (EI): m/z = 226 (M^+ + H, 23), 152 (54), 110 (100), 67 (5).

13b; yield: 250 mg (26%).

$C_{12}H_{19}NO_3$	calc.	C 63.97	H 8.52	N 6.22
(225.3)	found	64.35	8.29	6.18

^{1}H-NMR ($CDCl_3$): δ = 1.22–1.32 (m, 3 H); 1.45–2.28 (m, 8 H); 1.97, 2.12 (2 s, ratio 3.5:1, 3 H); 2.67–3.0 (m, 1 H); 4.12–4.27 (m, 2 H); 4.28–4.46 (m, 1.3 H); 4.58 (dd, ~ 0.7 H, J = 9, 3 Hz), (mixture of rotamers, ratio 3.5:1).

MS (EI): m/z = 226 (M^+ + H, 0.6), 152 (5), 110 (100), 82 (7), 67 (56).

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